

Effectiveness and Safety of Combination of Milk of Magnesia, Liquid Paraffin, and Sodium Picosulfate Oral Emulsion for Treatment of Chronic Constipation in Patients with Comorbidities

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ABSTRACT

Background: Chronic constipation in patients with type 2 diabetes mellitus (T2DM), hypothyroidism, and hypertension significantly impact quality of life. Evidence supporting combination laxative therapy in this population remains limited. This pilot study evaluated the effectiveness, safety and tolerability of a fixed-dose oral emulsion containing milk of magnesia, liquid paraffin, and sodium picosulfate. **Methods:** In this prospective, single-arm, 50 adults with chronic constipation and T2DM, hypothyroidism, and/or hypertension received the fixed-dose combination of milk of magnesia, liquid paraffin, and sodium picosulfate for a period of 8 weeks. Effectiveness was assessed using the Patient Assessment of Constipation Symptoms (PAC-SYM) and Quality of Life (PAC-QoL) questionnaires, alongside weekly spontaneous bowel movements (SBMs). Safety evaluations included adverse event (AE) monitoring, tolerability assessment and serum magnesium measurements. **Results:** PAC-SYM scores decreased significantly at Week 8 (2.45 ± 0.78 to 0.32 ± 0.14 ; $p < 0.0001$), and weekly SBMs increased (5.82 ± 4.31 to 14.66 ± 3.55 ; $p < 0.0001$). PAC-QoL scores improved significantly (68.86 ± 15.90 to 33.45 ± 6.39 ; $p < 0.0001$). Treatment was excellent for 90% of participants. One participant (2.0%) experienced mild, treatment-unrelated diarrhea. No serious AEs were reported. Serum magnesium levels decreased slightly from 1.97 to 1.87 mg/dL ($p = 0.005$), but remained within clinically acceptable limits. **Conclusion:** The fixed-dose triple-combination laxative significantly improved constipation symptoms, bowel frequency, and quality of life in patients with metabolic and cardiovascular comorbidities, warranting validation in larger randomized controlled studies. **Clinical Significance:** This combination offers a highly effective and safe management strategy for chronic constipation in complex patients with T2DM, hypothyroidism, and hypertension.

Keywords: Chronic constipation; Type 2 diabetes mellitus; Hypothyroidism; Hypertension; Laxatives; Quality of life.

Chronic constipation is described as continuing difficulty with infrequent or incomplete bowel movements without secondary causes. It includes functional, idiopathic, and secondary types^{1,2}. It affects 10-20% of adults worldwide and the prevalence is higher among older adults and those with other health conditions³⁻⁵. In Asia, constipation is a significant public health issue⁵. It is severe in patients with type 2 diabetes mellitus (T2DM), hypothyroidism,

and hypertension. Diabetes can slow colonic movement and affect coordination, while hypothyroidism slows gut motility due to reduced metabolic activity^{2,4}. Hypertension may increase the risk of heart problems like arrhythmia or fainting due to straining⁴. Treatment usually follows a stepwise plan recommended by the American Gastroenterological Association (AGA) and American College of Gastroenterology (ACG), starting with lifestyle changes and moving to bulk-forming agents, osmotic laxatives, lubricants, and stimulants^{6,7}. Chronic constipation also leads to important economic and personal burdens, with decreased quality of life and increased healthcare use³.

Even with established treatment plans, current approaches often do not work well for patients who have

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metabolic and cardiovascular conditions. These health issues change the pathophysiology of constipation: diabetic autonomic neuropathy slows the colonic transit; hypothyroidism weakens peristaltic activity, and cardiovascular risk makes straining difficult^{2,8,9}. These patients are usually prescribed several medications like antihypertensives, antidiabetic agents, and thyroid supplements, which may interact with and complicate the laxative therapy^{5,10}.

Monotherapy generally targets a single mechanical pathway, whether bulk-forming, osmotic, or stimulant, and often fails to treat moderate to severe or complex constipation^{6,8}. A bulk-forming agent may worsen bloating and abdominal discomfort in a diabetes patient with gastroparesis; stimulants alone may cause cramping and urgency in vulnerable patients, and osmotic agents may sometimes fail to adequately address the hard stool consistency and slow transit in hypothyroidism¹⁰. Likewise, polypharmacy and having less physiological reserve in middle-aged and older adults causes susceptibility to adverse events and electrolyte disturbances. This highlights the need for safer treatments that complement different therapeutic approaches^{9,10}.

A fixed-dose oral emulsion combining milk of magnesia (osmotic laxative), liquid paraffin (lubricant), and sodium picosulfate (stimulant prodrug) offers an approach to deal with multifactorial constipation with different mechanisms. Milk of magnesia helps retain water in the stool to make it bulkier and softer, liquid paraffin provides emollient facilitation for easy passage, and sodium picosulfate stimulates the myenteric plexus to improve the propulsive colonic activity^{8,11}. Sodium picosulfate alone has been shown to improve bowel movement frequency and quality of life in randomized controlled trials (RCTs)^{12,13}. While each of these agents are commonly used in clinical practice, evidence on fixed-dose triple combinations (FDCs) is very limited, particularly in comorbid populations^{8,9}. Newer prescription drugs, including prucalopride, lubiprostone, and linaclotide are available, but cost and access often limit their use in India, so practical treatment options are still needed^{14,15}. In patients with chronic constipation and comorbidities such as T2DM, hypothyroidism, and/or hypertension, fixed-dose triple-combination laxative therapy has not been evaluated in prospective studies. Most clinical trials of sodium picosulfate and other laxatives largely excluded patients with significant comorbidities or polypharmacy, limiting generalizability to routine practice^{5,9}. There is also limited safety data on magnesium-containing laxatives

in patients with metabolic comorbidities, and serum magnesium monitoring in this population is also rarely reported in prospective trials⁸. In addition, detailed patient-reported outcome data using validated tools like the Patient Assessment of Constipation Symptoms (PAC-SYM) and Patient Assessment of Constipation Quality of Life (PAC-QoL) questionnaires for combination laxative regimens in comorbid Asian and Indian populations are lacking^{12,13}.

This prospective, single-arm pilot study aims to provide evidence on the effectiveness and safety the study product for patients with these health conditions. The study used standard patient-reported outcome tools (PAC-SYM, PAC-QoL) and tracked objective measures such as the number of spontaneous bowel movements per week to assess symptoms and improvement^{12,13}.

Importantly, the study also monitored blood magnesium levels to address safety concerns in patients with polypharmacy. The results are meant to help physicians make practical treatment decisions for patients who have not responded well to single-drug therapy, in line with current guidelines that stress evidence-based care⁷.

MATERIALS AND METHODS

Study Design

This was a single-arm, pilot study conducted in 50 subjects with chronic constipation and co-morbidities like T2DM, hypothyroidism, and hypertension. Eligible subjects who provided written informed consent were enrolled in the study and their participation spanned for 8 weeks. During the study, they received a combination of Milk of Magnesia, Liquid Paraffin, and Sodium Picosulfate. The effectiveness and safety of the oral emulsion was evaluated throughout the study period [CTRI No. - CTRI/2025/03/083129].

KIMS Ethics Committee approved the study on 16 December 2024 and all the study-related activities commenced only after the approval from the committee.

Setting

The study was conducted in Krishna Institute of Medical Sciences, Hyderabad, from 9th August 2025 to 6th March 2026. Enrolled subjects were requested to attend all three site visits and were followed up telephonically every week for compliance and status.

Eligibility Criteria

Men and women of 18 to 65 age, with chronic constipation and had a diagnosis of T2DM,

hypertension, or hypothyroidism, confirmed by test reports from the past six months were included in the study. Participants were excluded if they had taken the study product within two weeks before enrollment, had hypersensitivity to the study product or its excipients, or conditions affecting gastrointestinal motility, bowel disease, gastrointestinal obstruction or perforation, a history of gastrointestinal surgery with painful abdominal symptoms, hepatic or renal dysfunction, psychiatric conditions, or active malignancies. Pregnant and lactating women were also excluded.

Study Endpoints & Assessments

The primary objective was to determine effectiveness using PAC-SYM score and the number of spontaneous bowel movements. Secondary objectives were PAC-QoL score, safety and tolerability. This was determined by the number and percentage of patients with adverse drug reactions. Serum magnesium levels were measured as an exploratory objective. Diarrhea or loose stools and patient compliance were also monitored.

Study Size

Since this was a pilot study, no formal sample size calculation was done and a total of 50 eligible subjects were enrolled in the study.

Statistical Analysis

As this was a pilot study, we did not conduct a formal sample size calculation. We enrolled 50 eligible patients with chronic constipation and comorbidities. Continuous variables were summarized as mean and standard deviation or as median with range, as appropriate. Categorical variables were shown as frequencies and percentages. We used paired t-tests to analyze changes from baseline in PAC-SYM scores, and repeated-measures ANOVA to examine changes in spontaneous bowel movements, PAC-QoL scores, and serum magnesium levels during study visits. Safety outcomes like adverse events, physical exam findings, vital signs, and lab results, were described. A two-sided P value below 0.05 was considered statistically significant.

RESULTS

Patient demographics and baseline characteristics

Demographics

Forty-seven of the 50 subjects enrolled completed the study. Two were lost to follow-up and 1 withdrew due

to an adverse event (diarrhea/loose stools). The mean age was 50.3 years. Most participants were men (64%) and Asian (98%), while 2% were African or Black. Disposition and baseline demographics are presented in Figure 1 and Table 1, respectively.

Comorbidities

Metabolic and cardiovascular disease history was significant in the study population. The most prevalent disease was hypertension, which was seen in 27 subjects (54.0%) followed by T2DM and hypothyroidism in 21 subjects (42.0%) each. These conditions frequently overlapped, with 16.0% of subjects having both hypertension and T2DM, 8.0% having hypertension, T2DM, and hypothyroidism, 4.0% having hypothyroidism and T2DM, and 2.0% having hypertension and hypothyroidism.

Only a small percentage of subjects had a history of previous cardiovascular or surgical history. Coronary artery disease (CAD) was present in 4.0% of the participants, while cholecystectomy and hysterectomy were each reported in 2.0% (Figure 2).

Impact of Treatment

Efficacy

The **PAC-SYM score** decreased significantly at each visit. The mean baseline score was 2.45 (± 0.783), which declined to 0.32 (± 0.144), representing a mean change of -2.13 (± 0.748 ; $p < 0.0001$) and an 86.01% reduction from baseline at the end of the study (Figure 3a).

Mean spontaneous bowel movements increased significantly from 5.82 (± 4.313) at baseline to 14.66 (± 3.553) at the end of the study, reflecting a 234.63% increase from baseline ($p < 0.0001$) (Figure 3b).

The **mean PAC-QoL score** improved from 68.86 (± 15.896) at baseline to 33.45 (± 6.389) at study completion, with a mean change of -35.68 (± 14.56 ; $p < 0.0001$), corresponding to a 49.31% reduction from baseline (Figure 3c).

Safety

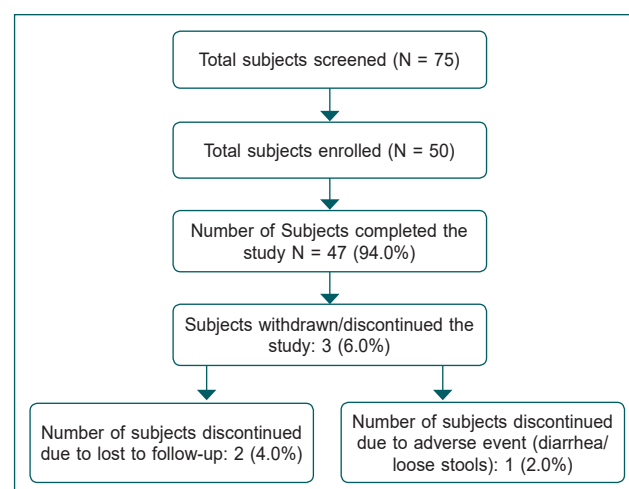
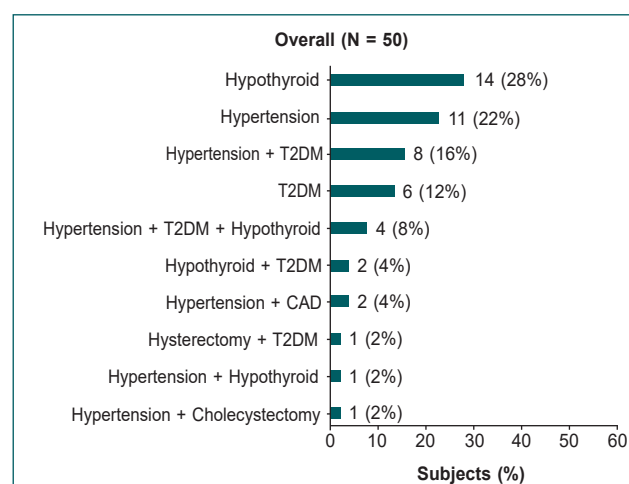
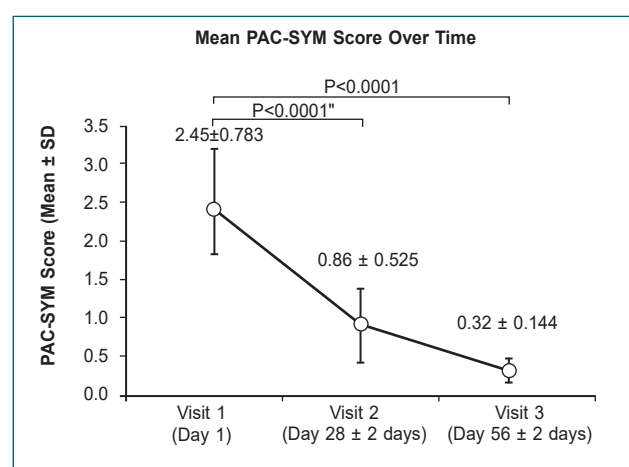
One subject had a mild, unrelated adverse event (diarrhea/loose stools) and fully recovered. No moderate or severe adverse events occurred. Serum magnesium levels changed from baseline to study end by -0.1 (0.235) ($P = 0.005$). Physical examinations and vital signs were stable throughout the study.

Overall, the study intervention was well tolerated. Most subjects (90.0%) rated tolerability as excellent, and 4.0%

Table 1. Summary of Subject Demographic Details

Characteristic	Category	Statistic	Overall (N = 50)
Age (years)		n	50
		Mean	50.3
		SD	8.77
		Median	51
		Minimum	28
		Maximum	65
Gender	Female	n (%)	18 (36)
	Male	n (%)	32 (64)
Race	Asian	n (%)	49 (98)
	Black or African American	n (%)	1 (2)
Height (cm)		n	50
		Mean	164.8
		SD	9.82
		Median	164.5
		Minimum	140
		Maximum	186
Weight (kg)		n	50
		Mean	73.9
		SD	12.75
		Median	71.5
		Minimum	54.9
		Maximum	114
BMI (kg/ m2)		n	50
		Mean	27.3
		SD	4.43
		Median	27
		Minimum	19.7
		Maximum	41.1
Lifestyle	Sedentary	n (%)	14 (28)
	Active	n (%)	33 (66)
	Physical activities	n (%)	3 (6)
Habitual	Never	n (%)	44 (88)
	Former	n (%)	3 (6)
	Current	n (%)	3 (6)
Dietary habits	Vegetarian	n (%)	12 (24)
	Non-Vegetarian	n (%)	1 (2)
	Both	n (%)	37 (74)

SD: standard deviation; N: Total number of subjects; n: The number of subjects in the specific category; %: calculated using N as the denominator (n/N*100).

**Figure 1.** Subject disposition.**Figure 2.** Comorbidities of study population (All Screened patients).**Figure 3a.** PAC-SYM Score. The mean baseline score was 2.45 (± 0.783), which declined to 0.32 (± 0.144) at the end of the study, representing a mean change of -2.13 (± 0.748)
Visit 2: ~64.5% reduction
Visit 3: ~86.9% reduction

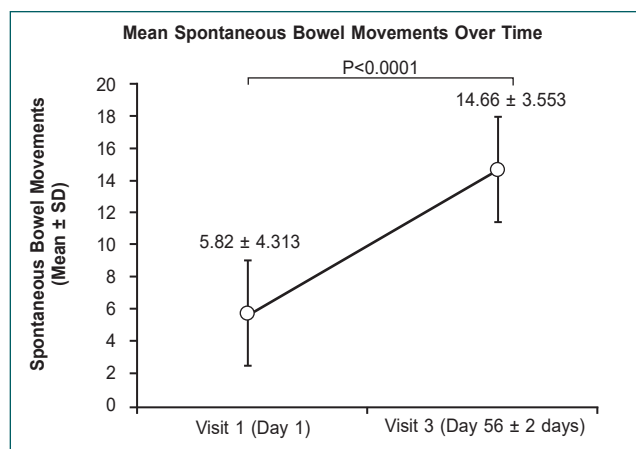


Figure. 3b. Mean spontaneous bowel movements increased significantly from 5.82 ($\pm$ 4.313) at baseline to 14.66 ($\pm$ 3.553) at the end of the study.

Baseline mean: 5.82/week

Visit 3 mean: 14.66/week

Mean increase: +9.23/week

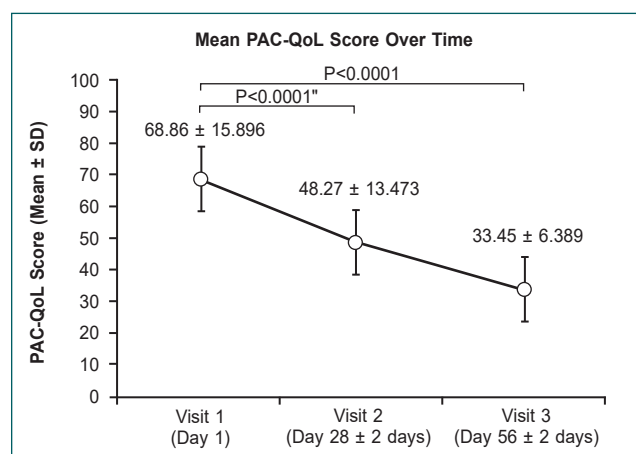


Figure. 3c. The mean PAC-QoL score improved significantly, decreasing by 35.68 points from 68.86 $\pm$ 15.90 at baseline to 33.45 $\pm$ 6.39 at study completion. Progressive decline demonstrates sustained and clinically meaningful QoL improvement

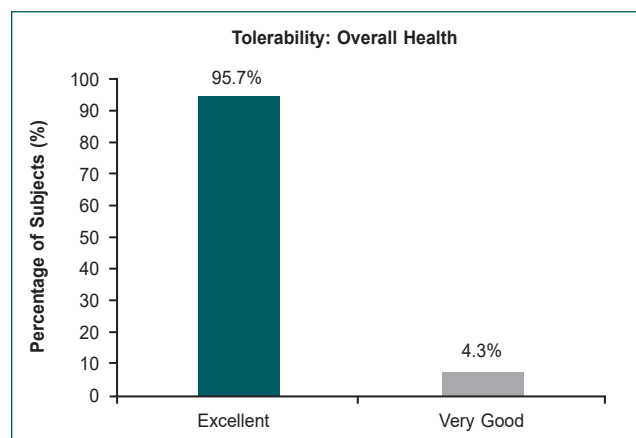


Figure 4. Study product tolerability.

reported very good tolerability. Tolerability data were unavailable for 6.0% of participants (Figure 4).

DISCUSSION

Chronic constipation is frequently seen in patients with metabolic and cardiovascular comorbidities. In the present study, the majority of subjects had hypertension, diabetes mellitus, or thyroid disorders that are well known to co-occur with constipation and that can complicate pharmacological management because of altered gut motility or polypharmacy¹.

Patients experienced a marked reduction in the constipation symptom severity. Mean PAC-SYM scores decreased from 2.45 at baseline to 0.32 at the final visit. This improvement is greater than that reported in large RCTs of newer prokinetic agents. In pooled analyses of six prucalopride trials, mean PAC-SYM total scores improved from about 1.9 at baseline to 1.2-1.4 at the final treatment assessment, while the proportion of patients achieving a clinically meaningful improvement ranged from 24% to 38%¹⁶. The present study observed a mean reduction of 2.13 points, with scores approaching the bottom of the scale. These findings demonstrated a considerable improvement in symptoms. However, comparisons with other studies should be interpreted cautiously because of differences in study design, baseline characteristics, study duration, and the single-arm design of the present study.

Mean spontaneous bowel movements increased from 5.82 to 14.66 per week. This outcome compares favorably with published data on sodium picosulfate monotherapy, where meta-analyzed mean differences versus placebo of approximately 4.0 spontaneous bowel movements per week (95% CI 2.37-5.71)[17]. In the sodium picosulfate RCT by Mueller-Lissner et al, mean complete spontaneous bowel movements increased from 0.9 at baseline to 3.4 per week with active treatment, compared to 1.1 to 1.7 with placebo¹⁸. The higher absolute frequency observed in the present study likely reflects the combined effects of the osmotic and lubricant components with the stimulant, as well as differences in baseline bowel habits between study populations.

Quality of life improved markedly, with mean PAC-QoL scores decreasing from 68.86 to 33.45. Meta-analyzed data for sodium picosulfate report a mean difference in PAC-QoL score versus placebo of 0.65 (95% CI 0.50-0.80) on the original 0-4 scale¹⁷. In the bisacodyl and sodium picosulfate trials by Mueller et al, active treatment produced greater improvement

than placebo across all PAC-QoL domains, with 50.3% of treated patients reporting satisfaction with their stool pattern compared to 12.8% in the placebo group². The magnitude of improvement observed in the present study, with the total PAC-QoL score reduced by more than half, suggests a substantial quality-of-life benefit. However, the absence of a control arm limits definitive interpretation of these findings.

The safety profile is favorable, with only one mild adverse event (diarrhea, 2.0%) reported, which resolved after discontinuation of the study medication. This incidence is considerably lower than that reported in RCTs of stimulant laxatives, where diarrhea has been observed in 32-53% of patients treated with bisacodyl or sodium picosulfate, while abdominal pain has been reported in 6-25% of cases. The lower incidence of diarrhea observed in the present study may be attributable to the combination formulation. The osmotic and lubricant components may have contributed to softer stool consistency, thereby reducing the cramping and urgency commonly associated with stimulant laxatives used as monotherapy. Similarly, serum magnesium levels were in the normal range throughout the study and consistent with the established safety profile of magnesium-containing laxatives in patients with normal kidney function⁶.

The major limitation of this study is its single-arm open-label design. Additionally, the small sample size and short follow-up period prevent assessment of long-term durability and delayed adverse events. As this was a single-center study, the findings may not be generalized.

CONCLUSION

This prospective, single-arm pilot study demonstrated that Cremaffin Plus oral emulsion significantly improved constipation symptoms, bowel movement frequency, and constipation-related quality of life in patients with chronic constipation and concomitant metabolic or cardiovascular comorbidities. Clinically meaningful improvements were observed in PAC-SYM and PAC-QoL scores, alongside an increase in spontaneous bowel movements to a mean of 14.7 per week, comparing favorably with outcomes reported for established laxatives and newer prokinetic therapies. The treatment was generally well tolerated and exhibited an **acceptable safety profile**, with only one mild adverse event deemed unrelated to study medication and no clinically significant changes in serum magnesium levels. These findings suggest that the fixed-dose combination of milk of magnesia,

liquid paraffin, and sodium picosulfate may represent an effective, well-tolerated, and practical therapeutic option for the management of chronic constipation in patients with comorbid conditions.

CLINICAL SIGNIFICANCE

The fixed-dose combination of osmotic, lubricant, and stimulant mechanisms provides a multimodal strategy to managing constipation by addressing stool consistency, intestinal transit, and bowel evacuation. This strategy may be especially useful for patients for whom increased stool frequency alone does not adequately alleviate constipation-related symptoms or quality-of-life impairment. The observed improvement and good tolerance in patients with metabolic or cardiovascular problems lend preliminary support to the combination as a potential therapy option. These findings add to the evidence for combination-based management of persistent constipation, complementing existing laxative and prokinetic medications.

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